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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/016,869	01/30/1998	DAVID H. BEACH	GPCI-P10-071	7533

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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/20/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/016,869	Applicant(s) BEACH ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2001 and 05 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,58-77 and 79-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,58-77 and 79-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The request filed on 9/5/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/016,869 is acceptable and a CPA has been established. An action on the CPA follows.

2. The Examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Jessica Roark, Art Unit 1644, Technology Center 1600.

3. Applicant's amendment, filed 5/29/01 (Paper No. 27), is acknowledged.
Claims 1, 10 and 78 have been canceled. Claims 2-9 and 12-57 have been canceled previously.
Claims 79-82 have been added.
Claims 11, 58-60, 65-67, 71 and 77 have been amended.
Claims 11, 58-77 and 79-82 *are pending.*

4. Applicant's arguments with respect to the pending claims have been considered but are moot in view of the new grounds of rejection.

5. Sequence compliance: The CRF, paper copy of the Sequence Listing and Statement that the CRF and Sequence Listing are identical, filed 6/5/00, has been found acceptable and entered.

However,
6. The specification is objected to under 37 CFR 1.821(d) because the SEQ ID NOS are not disclosed in the specification adjacent referenced sequences (for example, sequences appear on pages 32-33 of the instant specification that appear to corresponds to SEQ ID NOS:15-17, but that lack identifiers). Appropriate correction is required.

7. Priority claim: The Declaration and first line of the specification indicate that the instant application is either a continuation or continuation-in-part of several earlier applications.

USSN 08/227,371 and USSN 07/991,997 were not available to the Examiner.
Applicant on 10/25/00 (Paper No. 18) provided a copy of the specification of USSN 08/154,915.
PCT/US93/09945 has been considered only on the basis of WO94/09135.

The current Examiner has evaluated written support for individual subject matter as indicated below:

	'869 (instant)	'915	WO94
antibodies to "p16"	page 33	page 27	page 22
Fab	page 33	no	no
F(ab')2	page 33	no	no
monoclonal Ab	page 33	page 27	page 22
purified polyclonal Ab	page 33	no	no
antisera	page 33	page 27	page 22
p16 antibody kit	not found	page 28	page 23
labeled p16 antibody	not found	page 29	page 24
hybridization conditions	page 17	no	no
p16 of 148 amino acids	no	SEQ ID NO:4	SEQ ID NO:4
p16 of 156 amino acids	SEQ ID NO:2	no	no

USSN 08/248,812 appears to provide the same support as the instant specification.

Based upon this analysis, claims 58-77, 79-80 and 82 do not appear to be entitled to the filing dates of the '915 or PCT applications; either because they directly or indirectly recite SEQ ID NO:2, hybridization conditions, antibody fragments, or purified polyclonal antibodies.

Applicant is invited to point out adequate written support for these instant limitations.

8. The Abstract of the invention is not descriptive. A new Abstract is required that is clearly indicative of the invention *to which the claims are directed.*

In addition, Applicant should avoid the use of novel in the Abstract, as patents are presumed to be novel and unobvious.

9. The Title of the invention is not descriptive. A new Title is required that is clearly indicative of the invention *to which the claims are directed.*

10. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required if the application is allowed. Applicant is reminded that the "Brief Description of the Drawings" should be amended to reflect any changes introduced with the formal drawings.

11. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

12. Claim 59 and dependent claims 61-63 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. An antibody reactive with the class of proteins encompassed by the term "cell cycle regulatory protein" is broader in scope than an antibody that reacts with a p16 protein.

13. Claim 64 and 69-70 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. A "labeled" antibody is broader in scope than the isolated antibody of the independent claim.

14. Claims 11, 58, 61 and dependent claims 61-64, 79 and 81 are objected to under 37CFR 1.821(d) for failing to recite the SEQ ID NOS. in the claims. (*Please see additional comments below regarding incorporation by reference*).

15. Claim 76 is objected to because of the following informalities: it appears the last phrase of the claim was intended to read -- in samples *of* cells -- rather than "in samples *in* cells". Appropriate correction is required.

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 64, 68-76 and 82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed. *This is a New Matter rejection for the following reasons*:

The specification as-filed does not appear to provide an adequate written description of either a "labeled antibody" (claims 64 and 69) or a "kit comprising an isolated anti-CCR antibody" (claims 68-76 and 82).

The specification as filed does not provide an adequate written description or set forth the metes and bounds of the phrases "labeled antibody" and "kit comprising an isolated anti-CCR antibody". The specification does not provide blazemarks nor direction for the above-mentioned "labeled antibody" and "kit comprising an isolated anti-CCR antibody", as they are currently recited. While it is noted that a diagnostic kit comprising an *anti-p15* antibody is recited in original claim 41, a species does not support a claim to a genus. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Obviousness is not the standard for the addition of new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977). New Matter is a written description issue.

Applicant is invited to clearly point out the written support for the instant limitations; otherwise, *Applicant is required to cancel the New Matter in the response to this Office Action.*

In addition, it is noted that the above limitations do appear to be supported in USSN 08/154,915 (e.g. on pages 28-29), and that USSN 08/154,915 is incorporated by references in the first line of the instant specification.

18. Claims 11, 58, 61-64, 66, 68-70, 72-76 and 79-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody to the p16 protein of SEQ ID NO:2, does not reasonably provide enablement for an antibody to:
a) *any* "p16 protein" that binds to *any* "cyclin dependent kinase" (e.g., claims 11 and 58);
b) *any* "cell cycle regulatory protein" (e.g., claim 68); or
c) *any* "p16 protein" encoded by a nucleic acid sequence that hybridizes at conditions of 2xSSC and 50 degrees or higher stringency to SEQ ID NO:1 (e.g., claims 59 and 66).
The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses the p16 protein of SEQ ID NO:2 that binds specifically to the cyclin-dependent kinase CDK4 (e.g., pages 51-53 and Example 2 on pages 58-59). The specification also discloses antibodies to p16 and two other cell cycle regulatory proteins p13.5 and p15 (e.g., page 33). The state of the art at the time the invention was made recognized that there were several cyclin dependent kinases (CDK), including CDK4, as also disclosed in the specification (e.g., page 11, especially 1st full paragraph).

The instant claims encompass in their breadth an antibody to *any* "p16" protein that binds to *any* cyclin-dependent kinase. The specification appears to disclose a single "p16" protein, that of SEQ ID NO:2, and only a single cyclin-dependent kinase to which it binds, CDK4. "A p16 protein" encompasses any protein with that molecular weight. It was well known to the skilled artisan at the time the invention was made that an assignment of molecular weight was at best approximate; therefore a recitation of "p16" without more does not appear to provide sufficient structural features to allow the skilled artisan to determine if a protein belongs to the genus of "p16" proteins. Further, it was know in the art at the time the invention was made that there were several cyclin-dependent kinases. Thus in the absence of a testable function, such as binding to a *specific* CDK, the instant claims do not appear to provide sufficient guidance as to which proteins are encompassed by the instant claim limitations. Given the large number of proteins of an approximate molecular weight of 16kD and multiple CDKs; the skilled artisan would not have a reasonable expectation that any protein meeting the limitation 16kD would bind a cyclin-dependent kinase. Therefore, it would require undue experimentation of the skilled artisan to determine if a protein met the instant claim limitations and then produce an antibody to that protein.

Similarly, the recitation of a "cell cycle regulatory protein" encompasses *any* protein with that function. However, Applicant does not appear to have provided the requisite structural features that would allow the skilled artisan to make and use an antibody to a "cell cycle regulatory protein" commensurate in scope with the instant claims. Further, regulatory cell cycle regulatory proteins can have opposing functions, as some proteins may stimulate progression though the cell cycle, whereas others would inhibit cell cycle progression (e.g., Xiong et al. Genes & Dev. 1993; 7:1572-1583, IDS #EO). While "cell cycle regulatory protein" may have some notion of the activity of these molecules, claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make and use such molecules commensurate in scope with the claimed invention. In turn, without sufficient guidance as to the identity and function of a protein, it would likewise require undue experimentation of the skilled artisan to make and use antibodies to the proteins and kits comprising such antibodies.

With respect to p16 proteins encoded by a nucleic acid sequence that hybridizes at conditions of 2xSSC and 50 degrees or higher stringency to SEQ ID NO:1; the skilled artisan recognized that depending upon the hybridization conditions used, whether or not hybridization occurs over the full length of the target sequence and whether a functional activity was shared between the target sequence and the probe; extensive variation can be encompassed by hybridization language.

In the instant case the hybridization conditions recited are low stringency, no minimal length is required, nor is there a functional activity associated with the hybridizing nucleic acids; thus, the skilled artisan would expect highly divergent sequences to hybridize and would not reasonably expect that these hybridizing sequences would encode proteins with a function similar to that of p16. Even single amino acid changes can alter the function of a protein. For example, Voet et al. (In Biochemistry. John Wiley & Sons. 1990, Vol.1, pages 126-128, and page 230) teaches that a single Glu to Val substitution in the β subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals (i.e., those in which both alleles encode the sickle-cell variant), erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-127 and page 230, paragraph bridging columns in particular). Given that proteins differing in only a single amino acid can have drastically different functions; it would require undue experimentation of the skilled artisan to determine which of the many proteins encoded by a nucleic acid sequence that hybridizes at conditions of 2xSSC and 50 degrees or higher stringency to SEQ ID NO:1 would have the same function as the instant p16 protein of SEQ ID NO:2. Therefore it would require undue experimentation to make and use antibodies to these diverse proteins.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, it would be unpredictable as to which members of the genus of "p16 proteins", the genus of "cell cycle regulatory proteins" or the genus of polypeptides encoded by a nucleic acid sequence that hybridizes at conditions of 2xSSC and 50 degrees or higher stringency to SEQ ID NO:1 would have similar activities to the p16 protein of SEQ ID NO:2. In turn, it would be unpredictable as to how to make and use antibodies to these different molecules. Thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

19. Claims 11, 58, 61-64, 66, 68-70, 72-76 and 79-82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The claims recite antibodies and kits comprising antibodies to
a "p16 protein" that binds to *any* "cyclin dependent kinase" (e.g., claims 11 and 58);
a "cell cycle regulatory protein" (e.g., claim 68); and
a"p16 protein" encoded by a nucleic acid sequence that hybridizes at conditions of 2xSSC and 50 degrees or higher stringency to SEQ ID NO:1 (e.g., claims 59 and 66).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

The specification discloses the p16 protein of SEQ ID NO:2 that binds specifically to the cyclin-dependent kinase CDK4 (e.g., pages 51-53 and Example 2 on pages 58-59). The specification also discloses antibodies to p16 and two other cell cycle regulatory proteins, p13.5 and p15 (e.g., page 33). The claims are drawn to a genus of antibodies which are specifically reactive with proteins related to p16 (those encompassed by the phrase "a p16 protein which binds a cyclin dependent kinase" and "a p16 protein encoded by a nucleic acid that hybridizes") or proteins that are cell cycle regulatory proteins, which includes the p16 protein of SEQ ID NO:2. The essential feature of the instant claims appears to be the p16 protein of SEQ ID NO:2 to which an antibody is specifically reactive. However, Applicant does not appear to have provided functional characteristics coupled with a known or disclosed *correlation between function and structure* for either related "p16 proteins", or the genus of "cell cycle regulatory proteins".

It is noted that a recitation of a molecular weight (i.e., p16 = a protein of 16kD) without additional structural information is by itself insufficient to distinctly claim a protein structure as a large number of amino acid sequences having unrelated function are encompassed by such a recitation. In addition, there does not appear to be a *specific* functional activity recited for these various proteins recognized by the antibodies. Binding to a "cyclin-dependent kinase" is not a specific and testable function because there are several cyclin-dependent kinases. Similarly, an activity as a cell cycle regulatory protein without more does not provide a functional characteristic because this broad "function" is shared by many different proteins and does not correlate with a particular structure.

Therefore, one of skill in the art would not recognize the Applicants to be in possession of either any "p16 protein" or "cell cycle regulatory proteins", or antibodies to these proteins as encompassed by the claimed invention. Consequently, the claimed invention is not described in such a way as to reasonably convey to one of ordinary skill in the art that the inventor, at the time the application was filed, had possession of the invention. See Regents of the University of California v. Eli Lilly & Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Applicant is also directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

20. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 11, 58, 61-64, 66, 71 and 79-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 11, 58, 66, 82 and dependent claims 61-64 and 79-81 are indefinite in that they only describe the compositions of interest by an arbitrary protein name, "p16". Others in the field may isolate the same protein and give it an entirely different name. While the instant claims do include the limitation that the "p16" protein specifically binds a cyclin-dependent kinase, this limitation is insufficient to distinctly identify a "p16" protein because there are several cyclin-dependent kinases. Further, in consideration of the discrepancies often encountered in the art between protein molecular weight; when a molecular weight is recited as a protein characteristic, the claims should include not only the method by which it was determined (e.g. SDS-PAGE, gel filtration, etc.), but also the conditions used (e.g., reducing, denaturing, etc.).

Applicant should particularly point out and distinctly claim the "p16" protein by claiming a sufficient number of characteristics associated with the "p16" protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.) to distinctly identify it. Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and of what compositions comprising that protein are made.

B) Claims 71 and 82 recite the limitation "the p16 protein". There is insufficient antecedent basis for this limitation in these claims because claim 68 from which they depend does not recite a p16 protein. Applicant should amend claim 68 to provide the proper antecedent basis.

C) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

22. As noted supra, instant claims 58-77, 79-80 and 82 do not appear to be entitled to the filing dates of the '915 or PCT applications; therefore, these claims are considered to have at earliest the priority date of USSN 08/248,812, i.e., 5/25/94.

Claim 11 does appear to be entitled to at least a filing date of 10/18/93.

The art rejections have therefore been applied accordingly.

Please see concluding comments regarding incorporation by reference in view of the objections and rejections set forth above and the art rejections set forth below.

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.

24. Claims 58-77, 79-80 and 82 are rejected under 35 U.S.C. 102(e) as being anticipated by Kamb (US Pat No. 6,090,578, see entire document).

Kamb teaches and claims an antibody which binds a mammalian MTS1 polypeptide (see entire document, including claims). Kamb also teaches that the MTS1 polypeptide and p16 are the same protein (see entire document; e.g. column 16, especially lines 53-65; column 38, especially lines 51-67; and SEQ ID NO:2). Kamb teaches that the p16/MTS1 protein is a cell cycle regulatory protein that binds the cyclin-dependent kinase CDK4 (see columns 43-45, especially column 44 at lines 13-35). As shown in SEQ ID NO:2 of Kamb, the MTS1/p16 protein differs from instant SEQ ID NO:2 only at positions 2 and 35, and this sequence is human (see entire document, e.g., Abstract). An antibody to SEQ D NO:2 of Kamb would also be specifically reactive with a p16 identical to instant SEQ ID NO:2, even though the two sequences are not "identical" (as recited in instant claim 77) because SEQ ID NO:2 of Kamb and instant SEQ ID NO:2 would inherently share the same antibody epitopes. In addition, SEQ ID NO:2 of Kamb meets the limitation of "has an amino acid of SEQ ID NO:2" since the two sequences are identical from residue 35 to 156. Further, the nucleotide sequence encoding SEQ ID NO:2 of Kamb would hybridize to instant SEQ ID NO:1 at conditions of 2xSSC and 50 degrees. Kamb teaches that the anti-MTS1/p16 antibodies may be polyclonal, monoclonal, or antibody fragments (e.g., columns 14-15 and 55-56); that the purified antibodies may be labeled with a detectable label (e.g., column 15 at lines 24-40 and column 27-28). In addition, Kamb teaches diagnostic kits for detecting the MTS1/p16 cell cycle regulatory protein comprising antibodies to the p16/MTS1 cell cycle regulatory protein; including sandwich assays in which a second antibody would be used to detect the anti-p16/MTS1 antibody (see especially columns 27-28 in view of columns 15 and 55-56).

Therefore the teachings of the reference anticipate the instant invention.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of antibodies to a p16/MST1 protein.

25. Claims 58-77, 79-80 and 82 are rejected under 35 U.S.C. 102(e) as being anticipated by Skolnick et al. (US Pat No. 5,624,819, of record; see entire document).

Skolnick et al. an antibody which binds a mammalian MTS1 polypeptide (see entire document). Skolnick et al. also teach that the MTS1 polypeptide and p16 are the same protein (see entire document; e.g. column 16, especially lines 43-54; column 38, especially lines 1-16; and SEQ ID NO:2). Skolnick et al. teach that the p16/MTS1 protein is a cell cycle regulatory protein that binds the cyclin-dependent kinase CDK4 (see columns 43-44, especially column 43 at lines 9-50). As shown in SEQ ID NO:2 of Skolnick et al., the MTS1/p16 protein differs from instant SEQ ID NO:2 only at positions 2 and 35, and this sequence is human (see entire document, e.g., Abstract). An antibody to SEQ D NO:2 of Skolnick et al. would also be specifically reactive with a p16 identical to instant SEQ ID NO:2, even though the two sequences are not "identical" (as recited in instant claim 77) because SEQ ID NO:2 of Skolnick et al. and instant SEQ ID NO:2 would inherently share the same antibody epitopes. In addition, SEQ ID NO:2 of Skolnick et al. meets the limitation of "has an amino acid of SEQ ID NO:2" since the two sequences are identical from residue 35 to 156. Further, the nucleotide sequence encoding SEQ ID NO:2 of Skolnick et al. would hybridize to instant SEQ ID NO:1 at conditions of 2xSSC and 50 degrees. Skolnick et al. teach that the anti-MTS1/p16 antibodies may be polyclonal, monoclonal, or antibody fragments (e.g., columns 14-15 and 54-55); that the purified antibodies may be labeled with a detectable label (e.g., column 15 at lines 20-31 and column 27). In addition, Skolnick et al. teach diagnostic kits for detecting the MTS1/p16 cell cycle regulatory protein comprising antibodies to the p16/MTS1 cell cycle regulatory protein; including sandwich assays in which a second antibody would be used to detect the anti-p16/MTS1 antibody (see especially column 27 in view of columns 15 and 54-55).

Therefore the teachings of the reference anticipate the instant invention.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of antibodies to a p16/MST1 protein.

26. Claims 68-70, 72-73 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Busch et al. (US Pat No. 4,794,077, see entire document).

Busch et al. teach and claim a kit comprising an antibody to a cell cycle regulatory protein (p145) and a detectable label for detecting the antibody (see entire document, especially claims 3-15 and column 11). Means for detecting the cell cycle regulatory protein are taught that include both a detectable label conjugated to the antibody (e.g. column 11 at lines 15-26 and claim 16) and a second antibody (e.g., column 11 at lines 27-41). Both monoclonal and purified polyclonal antibody preparations are taught (see entire document, especially claims 3-5 and 14-15). Busch et al. teach throughout the reference that the antibodies are formulated for detecting the protein in samples of cells (e.g., columns 7-8).

Therefore the teachings of the reference anticipate the instant invention.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of kit comprising antibodies to a cell cycle regulatory protein including p145.

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

28. Claims 11, 58-77 and 79-82 rejected under 35 U.S.C. 103(a) as being unpatentable over Xiong et al. (Genes & Dev. August 1993; 7:1572-1583, IDS #EO) in view of Busch et al. (US Pat No. 4,794,077).

The claims are drawn to antibodies, antibody preparations and kits comprising antibodies to a p16 cell cycle regulatory protein.

Xiong et al. teach a p16 cell cycle regulatory protein that binds the cyclin-dependent kinase CDK4 (see entire document, especially Figure 6 and page 1577). Xiong et al. teach that the molecular identity of p16 was unknown, but that it associates with proteins involved in cell cycle progression that are altered in oncogenically transformed cells, and that studies addressing possible altered responses involving cell cycle regulatory proteins are important to understanding oncogenesis (e.g., see "Discussion"). Xiong et al. purify p16 from several human cellular sources and provide a peptide map to show that p16 is the same in each case (e.g., Figure 8). Xiong et al. also teach the production of antibodies to other proteins involved in cell cycle regulation (see entire document, especially "Antibodies and Immunological Methods" on page 1581), and use these antibodies to study the association and expression of various cell cycle proteins (see entire document).

Xiong et al. do not teach an antibody, antibody preparation, or kit comprising an antibody to p16.

Busch et al. have been discussed supra and teach antibodies, antibody preparations, and kits comprising antibodies to another cell cycle regulatory protein, p145 (see individual citations supra). Busch et al. also teach production of antibodies to cell cycle proteins by providing partial purified protein for use in immunization strategies (see especially columns 5-6). Busch et al. also teach that antibodies, antibody preparations, and kits comprising such antibodies are useful in the study of cell cycle regulatory proteins in tumor samples (e.g., columns 9-10).

Given the teachings of the references, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare antibodies, antibody preparations, and kits comprising antibodies to p16. Given the teachings of Xiong et al. that p16 is associated with CDK4 and involved in cell cycle progression and possibly the mechanism underlying oncogenesis, one of ordinary skill in the art would have been motivated to provide an antibody, antibody preparation, or kit comprising an antibody to p16 in order to study p16's role in cell cycle and oncogenesis. As taught by both Xiong et al. and Busch et al., one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of successfully producing antibodies to p16 and formulating them in various diagnostic kits for detecting p16 in a sample of cells. Although the amino acid sequence of p16 is not taught by either reference, the sequence in an intrinsic property of the protein and thus a recitation of sequence composition, either directly or in terms of hybridization language, does not render an antibody to the protein unobvious. Finally, although Fab and F(ab')2 fragments are not taught explicitly by either reference, these forms of antibodies were well known to one of ordinary skill in the art at the time the invention was made. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

29. Given the rejections and objections set for supra, it appears that it is essential that Applicant distinctly identify and provide and adequate written description of the p16 protein by reciting a sequence identifier.

However, it is noted that instantly disclosed SEQ ID NO:2 does not have an adequate written description in priority documents with a filing date that would be sufficient to overcome the rejections of record, as only a protein lacking the first 9 amino acids (SEQ ID NO:4) is disclosed in priority documents 08/154,915 and PCT/US93/09945 (as represented by WO94/09135).

As a possible means of obviating many of the rejections and objections of record, Applicant is invited to provide sufficient written support in the instant specification for the 148 amino acid sequence of p16 described in the priority documents to which incorporation by reference was made, and to amend the claims to refer to the p16 sequence supported in the priority documents.

If the 148 amino acid sequence of p16 is introduced into the instant specification; it *must also be included in the sequence listing and CRF* and provided a sequence identifier in order to comply with the sequences rules under 37 CFR 1.821 through 1.825 as follows:

> This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is reminded to amend the specification and claims to indicate the newly added SEQ ID NO.

If applicant provides sufficient written description and support for the p16 protein having the 148 amino acids sequence presented as SEQ ID NO:4 in the priority documents; then applicant is required to incorporate this essential subject matter for this particular sequence.

Regarding incorporation by reference, the following is noted:

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See In re Fouche, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

If Applicant incorporates by reference to parent USSN(s), Applicant is reminded that when the disclosure is amended to include the material incorporated by reference, the amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

30. No claim is allowed.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
November 16, 2001

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TC 1600
11/16/01